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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/690,198	10/16/2000	Douglas A. Collins	COP1002	2250

7590 03/12/2003

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EXAMINER

SHARAREH, SHAHNMAM J

ART UNIT

PAPER NUMBER

1617

DATE MAILED: 03/12/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/690,198	COLLINS ET AL.
	Examiner	Art Unit
	Shahnam Sharreh	1617

- The MAILING DATE of this communication appears on the cover sheet with the correspondence address -  
Period for Reply

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) Responsive to communication(s) filed on 09 December 2002.
- 2a) This action is FINAL.                  2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) 1-120 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1,3,5,7,9,12-15,18,20,24,49-51,55,56,60,61,111 and 112 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) All b) Some \* c) None of:  
1. Certified copies of the priority documents have been received.  
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) Notice of References Cited (PTO-892)  
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10
- 4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.  
5) Notice of Informal Patent Application (PTO-152)  
6) Other: \_\_\_\_\_

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2,4,6,8,10,11,16,17,19,21-23,25-48,52-54,57-59,62-110 and 113-120.

## **DETAILED ACTION**

Amendment filed on December 9, 2003 has been entered.

Claims 113 -120 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8. claims 2,4,6,8,10-11,16,19,21-23,25-48,52-54,57-59,62-110 are withdrawn because they do not read on the elected species. Claims 1,3,5,7,9,12-15, 18, 20, 24, 49-51, 55-56, 60-61, 111-112 are under consideration as they read on the elected species. Claim 18 depends on the non elected species.

Any rejection or objection that is not addressed in this Office Action is considered obviated in view of Applicant's arguments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Double Patenting***

Claims 1,3,5,7,9,12-15,18,20,24,49-51,55-56,60-61 stand provisionally rejected under the judicially created doctrine of double patenting over claims 1-28 of copending Application No. 10/027,593 for the reasons of record.

### ***Claim Rejections - 35 USC § 112***

Claims 1,3,5,7,9,12-15, 18, 20, 24, 49-51, 55-56, 60-61, 111-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependent claims thereof recite the term "residue" which renders the scope of the instant claims unclear. Specifically, it is not clear what type of residue is intended as the claimed subject matter. Accordingly, the metes and bounds of the claims are not clear.

***Claim Rejections - 35 USC § 102***

Claims 1, 3,5,12-13,15,18,20,24,49-51,55,56,111-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Russell-Jones et al US Patent 5,428,023 (Russell-Jones I).

Russell-Jones I discloses bioconjugates comprising a Vitamin B12 or its analogues complexed via a spacer or linker to a bioactive agent (Abstract). Vitamin B12 (or Cyanocobalamin) meets the limitations of formula I and contains a Cyano group at position X. The preferred agent used by Russell-Jones I is LHRH or interferons that are cytotoxic and used as chemotherapy (see col 2, lines 33-38; col 5, lines 60-68). Russell-Jones I uses a lysine-6 linker that cross-links to the carboxyl group of an acid-hydrolyzed propionamide side chain adjacent to ring A, B or C of the Vitamin B. Thus, meeting the limitations of claim 3, 5,15,18, 20, 51, and 56. Since Russell-Jones's linker meets the limitations of the instant linkers, they inherently meet the length limitations of the instant spacers claimed in angstroms. Finally, Russell-Jones teaches oral formulations for specific therapeutic use. Therefore, Russell-Jones I anticipates the limitations of the instant claims.

Claims 1, 3,5,7,9,12-13,15,18, 20, 24,49-51,55,56,61,111-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Russell-Jones et al (Bioconjugate Chem 1995, 6, 459-465) (Russell-Jones II) or US Patent 5,,548,064 (Russell-Jones III).

The teachings of Russell-Jones II and III are substantially similar to Russell-Jones I except that it further discloses linker at ring e of the Vitamin B12 (abstract). Further, Russell-Jones II explicitly exemplifies his Linkers set forth in Figure 1 and Table 1 (see pages 460-462; 464 1<sup>st</sup> col and 2<sup>nd</sup> col lines 1-20). The linkers used in Russell-Jones II, carbidoimido, diaminoethane, diaminohydroxypropane, diaminodithiahexane meet the limitation of the instant linkers where at least A is an alkyl, and W and Q are independently -N (R) C(=O)-, or -C(=O)N(R),-S-, -N(R)-, O-CO or a direct bond and R is independently H or (C1-C6) alkyl. Therefore, Russell-Jones II anticipates the limitations of the instant claims.

Russell-Jones III is substantially the same as Russell-Jones II, but it explicitly shows the type of spacers employed in his vitamin B12 conjugates (see col4-5; col 8, lines 40-col9, lin26; col 11, lines 5-32). Russell-Jones III is anticipatory.

Claims 1, 3,5,7,9,12-13,15,18, 20, 24,49-51,55,56,61,111-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Pathare et al (Bioconjugate Chem 1996, 7, 217-232).

Pathare discloses bioconjugates comprising cyanocobalamin and biotin (abstract). Figure 1 of Pathara teaches which sites can Vitamin B 12 be conjugated. Accordingly, Pathare teaches conjugations at rings A, B, C, D, and E. (see figure I). Pathare also discloses such conjugates with Cyanocobalamin where a diamine and

alkylamine linkers are used (see table 1, specially compounds 5, 9, 13, 15, page 224, 228-230). Therefore, Pathare anticipates the limitations of the instant claims.

Claims 1,3,5,7,9,12-15, 18, 20, 24, 49-51, 55-56, 60-61, 111-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pathare et al in view of Grissom et al US Patent 6,315,978.

The teachings of Pathare are discussed above. Pathare fails to use a doxorubicin as the drug of choice, but suggests that many other antineoplastic agents such as 5-FU or methotrexate have been conjugated with Vitamin B12 derivatives.

Grissom teaches Vitamin B 12 bioconjugates (abstract, col 37-38). Grissom explicitly enumerate doxorubicin as a drug of choice for conjugating it to Vitamin B12 (see col 8, lines30-33, col 27-col32). Grissom teaches various types of linkers that may be employed to link his drugs to the vitamin B 12 moiety (see col 10, line 26-col 11, line 20, col 60, claims 1, 7). Grissom teaches that the nature of the spacer is not critical to the invention, and that a skilled artisan will readily recognize other spacers which can be used to link bioactive components to form a bioconjugate.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify Pathare's bioconjugates and attach a doxorubicin molecule at a ring of interest via a spacer of choice, as taught by Grissom, because as taught by Pathare and Grissom the ordinary skill in the art would have had a reasonable expectation of success in improving therapeutic benefits of a drug of choice when employing a linker between Vitamin B12 and the active drug molecule.

### ***Conclusion***

No claims are allowable at this time. The indicated allowability of claim 14 in the Attached Interview Summary is withdrawn in view of the new Grounds of Rejection. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

ss  
March 8, 2003

*[Signature]*  
RUSSELL TRAVERS  
PRIMARY EXAMINER  
GROUP 1200